Complete Summary

GUIDELINE TITLE

Ifosfamide-based combination chemotherapy in advanced soft tissue sarcoma: a clinical practice guideline.

BIBLIOGRAPHIC SOURCE(S)

Verma S, Younus J, Stys-Norman D, Haynes AE, Blackstein M, Sarcoma Disease Site Group. Ifosfamide-based combination chemotherapy in advanced soft tissue sarcoma: a clinical practice guideline. Toronto (ON): Cancer Care Ontario (CCO); 2006 Apr 11. 28 p. (Evidence-based series; no. 11-4). [40 references]

GUIDELINE STATUS

This is the current release of the guideline.

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Please visit the Cancer Care Ontario Web site for details on any new evidence that has emerged and implications to the guidelines.

COMPLETE SUMMARY CONTENT

SCOPE

DISEASE/CONDITION(S)

Inoperable locally advanced or metastatic soft tissue sarcoma

GUIDELINE CATEGORY

Assessment of Therapeutic Effectiveness
Treatment

CLINICAL SPECIALTY

Oncology

INTENDED USERS

Physicians

GUIDELINE OBJECTIVE(S)

- To evaluate whether combination chemotherapy regimens containing ifosfamide have an advantage in terms of response rate, time to progression, or survival, compared with similar regimens without ifosfamide, when used as first-line therapy in adult patients with inoperable locally advanced or metastatic soft tissue sarcoma
- To evaluate the adverse effects and effects on quality of life of ifosfamide-containing combination chemotherapy, compared with similar regimens without ifosfamide

TARGET POPULATION

Adult patients with inoperable locally advanced or metastatic soft tissue sarcoma

INTERVENTIONS AND PRACTICES CONSIDERED

Combination chemotherapy regimens containing ifosfamide

MAJOR OUTCOMES CONSIDERED

- Response rate
- Time to progression
- Survival
- Adverse effects
- Quality of life

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Hand-searches of Published Literature (Primary Sources)
Hand-searches of Published Literature (Secondary Sources)
Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

MEDLINE (1966 to July 2005), EMBASE (1980 to July 2005), and the Cochrane Library (2004, Issue 3) databases were searched. Disease-specific search terms

"sarcoma" (exploded Medical Subject Heading [MeSH] and text word) and "soft tissue" (as text words) were combined with treatment-specific terms "ifosfamide" (MeSH and text word), "ifosphamide," "iphosphamide," and "ifex" (text words). These terms were then combined with search terms for the following publication types and study designs: practice guidelines, systematic reviews, meta-analyses, randomized controlled trials, controlled clinical trials, phase II clinical trials, and phase III clinical trials.

In addition, conference proceedings of the American Society of Clinical Oncology (1997-Spring 2005) were searched for abstracts of relevant trials. The Canadian Medical Association Infobase (http://mdm.ca/cpgsnew/cpgs/index.asp) and the National Guideline Clearinghouse (http://www.guideline.gov/) were also searched for existing evidence-based practice guidelines.

Relevant articles and abstracts were selected and reviewed by one reviewer, and the reference lists from these sources were searched for additional trials, as were the reference lists from relevant review articles.

Inclusion Criteria

Articles were eligible for inclusion in this systematic review if they met both of the following criteria:

1. They were published reports or abstracts of randomized controlled trials (RCTs) comparing combination chemotherapy regimens containing ifosfamide with regimens without ifosfamide in adult patients with locally advanced or metastatic soft tissue sarcoma (STS).

   Although data from randomized controlled trials provided the primary evidence for this systematic review, single-arm phase II trials reporting on treatment with ifosfamide-containing combination chemotherapy regimens in adult patients with locally advanced or metastatic soft tissue sarcoma were also eligible. We also elected to examine the outcomes of phase II trials in order to obtain data on response and toxicity for different doses and schedules of ifosfamide-based treatment and on ifosfamide chemotherapy as second-line treatment, which were not available from the limited number of RCTs.

2. They reported data on time-to-progression or overall survival, in addition to the objective tumour response rate.

Exclusion Criteria

Articles were excluded if they were:

1. Trials of dose-intensive chemotherapy with growth factor or autologous bone marrow/stem cell transplant support (these will be included in a separate guideline)
2. Letters or editorials
3. Published in a language other than English
4. Trials of patients with pediatric sarcomas, Ewing's sarcoma, or bone sarcoma

5. Trials where patients were given concurrent radiotherapy or local regional modalities such as surgery, which might have influenced response or survival

NUMBER OF SOURCE DOCUMENTS

The literature search identified three randomized phase III trials and 23 single-arm phase II trials that met the inclusion criteria for this systematic review of the evidence.

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Expert Consensus (Committee)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Not applicable

METHODS USED TO ANALYZE THE EVIDENCE

Meta-Analysis of Randomized Controlled Trials
Systematic Review with Evidence Tables

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Synthesizing the Evidence

To estimate the effect of ifosfamide-containing combination chemotherapy on response rate and survival in patients with locally advanced or metastatic soft tissue sarcoma (STS), published data from randomized controlled trials (RCTs) were pooled in a meta-analysis by the guideline developers. Objective tumour response data (i.e., number of complete and partial responses) were obtained from the text of published trial reports, and one-year mortality data were extracted from published survival curves. The numbers of eligible patients were used as denominators for all pooled analyses. One year was selected as the time point at which to pool mortality data, because the expected median survival of patients with inoperable locally advanced or metastatic soft tissue sarcoma is nine to 12 months. Data were pooled and analyzed using the MetaView analysis component of the Cochrane Collaboration Review Manager 4.2 software. The results of the meta-analysis are expressed as a relative risk (RR) with a corresponding 95% confidence interval (CI). For tumour response, a relative risk <1.0 indicates that patients in the experimental treatment group (ifosfamide-based combination chemotherapy) had a higher probability of a complete or partial response compared with the control group (non-ifosfamide chemotherapy); conversely, a relative risk of response >1.0 favours the control group (non-ifosfamide chemotherapy).

For one-year mortality, a relative risk <1.0 indicates that the patients in the experimental treatment group (ifosfamide-based combination chemotherapy) experienced higher survival rates than the control group (non-ifosfamide chemotherapy). Data were analyzed using the random effects model (Mantel-

Haenszel). Heterogeneity was considered to be significant when p was less than 0.1 on the chi-square test for statistical heterogeneity.

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

This evidence-based series was developed by the Sarcoma Disease Site Group (DSG) of Cancer Care Ontario's Program in Evidence-based Care (PEBC). Evidence was selected and reviewed by one member of the PEBC Sarcoma DSG and methodologists.

The series is a convenient and up-to-date source of the best available evidence on ifosfamide-based combination chemotherapy for patients with inoperable locally advanced or metastatic soft tissue sarcoma (STS), developed through systematic review, evidence synthesis, and input from practitioners in Ontario.

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Not applicable

COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

METHOD OF GUIDELINE VALIDATION

External Peer Review
Internal Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

Report Approval Panel

Prior to submission of this evidence-based series report for external review, the report was reviewed and approved by the Program in Evidence-Based Care (PEBC) Report Approval Panel, which consists of two members, including an oncologist, with expertise in clinical and methodology issues. Key issues raised by the Panel were that the inclusion of the word "routine" in the recommendation created ambiguity in light of the compelling evidence demonstrating lack of benefit and that a rationale for using response as an important and policy-determining outcome was required, as was a rationale for including phase II studies, given the availability of three randomized controlled trials (RCTs). In response, the Disease Site Group (DSG) removed the word "routine", noted that response is an important outcome in this patient population given their limited treatment options, and noted that the inclusion of phase II studies reflected the previous

approach, of including both randomized controlled trials and phase II studies, at the time the report was initially started.

External Review

Following the review and discussion of Sections 1 and 2 of this evidence-based series, the Sarcoma DSG circulated the clinical practice guideline and systematic review to clinicians in Ontario for review and feedback. Feedback was obtained through a mailed survey of 74 practitioners in Ontario that included medical oncologists, radiation oncologists, and surgeons. The survey consisted of items evaluating the methods, results, and interpretive summary used to inform the draft recommendations and whether the draft recommendations should be approved as a practice guideline. Written comments were invited. The survey was mailed out on February 22, 2006. Follow-up reminders were sent at two weeks (post card) and four weeks (complete package mailed again). The Sarcoma DSG reviewed the results of the survey.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

In patients with metastatic soft tissue sarcoma, the addition of ifosfamide to standard first-line doxorubicin containing regimens is not recommended over single-agent doxorubicin. However, in patients with symptomatic, locally-advanced, or inoperable soft tissue sarcoma, in whom tumour response might potentially result in reduced symptomatology or render a tumour resectable, it is reasonable to use ifosfamide in combination with doxorubicin.

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The recommendations are supported by randomized phase III trials and single-arm phase II trials.

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

- A small, statistically significant improvement in tumour response rate was observed with ifosfamide-containing chemotherapy compared to non-ifosfamide-containing chemotherapy (relative risk, 1.52; 95% confidence interval, 1.11 to 2.08; p=0.009).
- Meta-analysis of published one-year mortality rates from three randomized trials did not detect a significant difference between ifosfamide and non-

ifosfamide-containing chemotherapy (relative risk, 0.98; 95% confidence interval, 0.85 to 1.13; p = 0.28).

POTENTIAL HARMS

Higher rates of adverse events, particularly grade 3-4 myelosuppression were observed in patients who received regimens that contained ifosfamide. A higher rate of toxic deaths was reported in two of the three randomized trials reviewed, for the ifosfamide-containing regimen.

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

- In combination with doxorubicin-containing regimen, the dose of ifosfamide should not exceed 7.5 g/m^2 given as either a split bolus or continuous infusion.
- Care has been taken in the preparation of the information contained in this document. Nonetheless, any person seeking to apply or consult the practice guideline is expected to use independent medical judgment in the context of individual clinical circumstances or seek out the supervision of a qualified clinician. Cancer Care Ontario makes no representation or guarantees of any kind whatsoever regarding their content or use or application and disclaims any for their application or use in any way.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Living with Illness

IOM DOMAIN

Effectiveness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

Verma S, Younus J, Stys-Norman D, Haynes AE, Blackstein M, Sarcoma Disease Site Group. Ifosfamide-based combination chemotherapy in advanced soft tissue

sarcoma: a clinical practice guideline. Toronto (ON): Cancer Care Ontario (CCO); 2006 Apr 11. 28 p. (Evidence-based series; no. 11-4). [40 references]

ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

2006 Apr 11

GUIDELINE DEVELOPER(S)

Program in Evidence-based Care - State/Local Government Agency [Non-U.S.]

GUIDELINE DEVELOPER COMMENT

The Program in Evidence-based Care (PEBC) is a Province of Ontario initiative sponsored by Cancer Care Ontario and the Ontario Ministry of Health and Long-Term Care.

SOURCE(S) OF FUNDING

Cancer Care Ontario
Ontario Ministry of Health and Long-Term Care

GUIDELINE COMMITTEE

Provincial Sarcoma Disease Site Group

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

For a current list of past and present members, please see the Cancer Care Ontario Web site.

FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

The members of the Sarcoma Disease Site Group disclosed potential conflicts of interest relating to the topic of this systematic review. No potential conflicts were declared.

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GUIDELINE AVAILABILITY

Electronic copies: Available in Portable Document Format (PDF) from the Cancer Care Ontario Web site.

AVAILABILITY OF COMPANION DOCUMENTS

The following are available:

- Ifosfamide-based combination chemotherapy in advanced soft tissue sarcoma: a clinical practice guideline summary. Toronto (ON): Cancer Care Ontario (CCO), 2006 Apr 11. Various p. (Practice guideline; no. 11-4). Electronic copies: Available in Portable Document Format (PDF) from the Cancer Care Ontario Web site.
- Browman GP, Levine MN, Mohide EA, Hayward RSA, Pritchard KI, Gafni A, et al. The practice guidelines development cycle: a conceptual tool for practice guidelines development and implementation. J Clin Oncol 1995;13(2):502-12.

PATIENT RESOURCES

None available

NGC STATUS

This NGC summary was completed by ECRI on June 22, 2006. The information was verified by the guideline developer on July 6, 2006.

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Date Modified: 10/2/2006